REMARKS

Status of the Claims

Claims 1-18 and 20 are pending.

Claims 1-16 and 20 have been amended.

Claim 22 was added.

Claims 19 and 21 have been canceled.

No new matter has been added by the instant amendments.

Reconsideration is respectfully requested.

Amendments to the Claims

Claims 1-16 were amended to delete the phrase "or prodrug" therefrom.

Claim 7 was also amended, at line 6 thereof, to delete the reference "A" from between the phrases "phenyl ring" and "at the 2."

Claim 15 was also amended, at line 2 thereof, to replace the misspelled term "hydrogn" with the term -- hydrogen --.

Claim 20 was amended, at line 1 thereof, to replace the term "The" with the term -- A -- and to replace the phrase "Claim 19 in which the inflammatory disorder is selected from" with the word -- treating --; at line 3 thereof, to remove the term "diabetes," therefrom; at line 4 thereof, to remove the terms "Alzheimer's disease," therefrom; at line 5 thereof, to insert a comma -- , -- after the word "ischemia" and to remove the phrase "and arthritis including" therefrom; and, at the last line thereof, to insert the word -- and -- between the terms "gouty arthritis," and osteoarthritis", and to replace the phrase "pain and neuropathy" with the text -- , comprising administering to a patient in need of such treatment a pharmaceutical composition according to Claim 17 --.

Claim 22 was inserted to list specific indications that match those taught in amended Claim 20 and to claim priority to Claim 18.

Claims 19 and 21 were canceled from the present application.

Applicants believe that the present amendments do not introduce new matter, are fully supported by the specification and priority document, and do not broaden the scope of the claims.

Rejections Under 35 U.S.C. §112, 2nd

Claims 1-21 were rejected under the second paragraph of 35 U.S.C. §112 as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner contends that recitation of the term "prodrug" in Claims 1-16 and 21 is allegedly indefinite. Applicants have amended Claims 1-16 to remove the term "prodrug" and have canceled Claim 21 such that this rejection should now be obviated and kindly removed.

For the above-stated reasons, applicants submit that the rejections under the second paragraph of 35 U.S.C. § 112 should be kindly withdrawn.

Rejections Under 35 U.S.C. §112, 1st

Claims 1-21 were rejected under the first paragraph of 35 U.S.C. §112 because the specification supposedly "does not reasonably provide enablement for making prodrug[s] of the claimed compounds." (10/17/05 O.A., p. 4.) As applicants stated in the previous section, Claims 1-16 were amended to delete the term "prodrug" and Claim 21 was canceled, so this rejection is now obviated and should be kindly removed.

Claims 19 and 20 were rejected under the first paragraph of 35 U.S.C. §112 for allegedly "not reasonably provid[ing] enablement for treating any or all inflammatory disorder[s] embraced in the instant invention." (10/17/05 O.A., p. 7.) Applicants have canceled Claim 19, amended Claim 20 and inserted Claim 22 in the manner described hereinabove, such that this rejection should be obviated. In particular, Claim 20 has been amended to remove the disorders "diabetes," "Alzheimer's disease," "arthritis," "pain" and "neuropathy" therefrom.

As requested by the Examiner, applicants will hereby provide support in the form of publications (attached herewith) to show that one skilled in the art would recognize that the instant specification would reasonably provide enablement for the disorders taught in Claims 20 and 22. Firstly, as disclosed in the instant specification and as discussed in applicants' responses to previous Office Actions, it is known by one skilled in the art that the p38 mitogen-activated protein kinase (MAPK) signalling pathway plays an important role in inflammation and other physiological processes. J. Saklatvala, "The p38 MAP kinase pathway as a therapeutic target in inflammatory disease," Current Opinion in Pharmacology, 2004, 4:372-377, 372; and J. Branger, et al., "Anti-Inflammatory Effects of a p38 Mitogen-Activated Protein Kinase Inhibitor During Human Endotoxemia," The Journal of Immunology, 168, 4070-4077 (2002). It is further known that specific inhibitors of the p38 MAPK's would empirically inhibit production of tumor necrosis factor (TNF)-α and interleukin (IL)-1 by lipopolysaccharide (LPS)-stimulated Cells. *Saklatvala* at 372. Hence, one skilled in the art would logically recognize that the presently claimed compounds would be expected to treat inflammatory–related diseases in general and the specific disorders discussed hereinbelow. In fact, Saklatvala states, "any inflammation strongly dependent upon the two primary cytokines (i.e., TNF-α and IL-1) will be reduced by p38 blockade." *Id.* at 376. Moreover, it is recognized that a "large body of evidence from preclinical studies indicates a crucial role of p38-α MAPK in inflammation." S. Kumar, et al., "p38 MAP Kinases: Key Signalling Molecules As Therapeutic Targets for Inflammatory Diseases," Nature Reviews: Drug Discovery, Vol. 2, Sept. 2003, 717-726, 722.

Not only has p38 inhibitor compounds been implicated in inflammatory disease in general, but such compounds, including the compounds taught in the instant invention, are known by those skilled in the art to be effective in treating the disorders identified in Claims 20 and 22.

TNF-α inhibitors are known to treat arthritis and psoriatic arthritis. P.J Mease, et al., "Psoriatic Arthritis Treatment: Biological Response Modifiers," Ann. Rheum. Dis., 2005, 64 (Suppl. II), ii78-ii82; and *S. Kumar*, et al. at 725. TNF-α inhibitors have been shown to reduce symptoms and signs of ankylosing spondylitis as well as improve the patients' quality of life while reducing serious toxicities. J.C. Davis, Jr., "Understanding the Role of Tumor Necrosis Factor Inhibition in Ankylosing Spondylitis," Seminars in Arthritis and Rheumatism, 34:668-677 (2004).

The TNF-α inhibitors Etanercept, Infliximals and Adalimumab, among others, have been shown to be effective in clinical trials to treat psoriasis patients. K.A. Papp, "The Long-term

Efficacy and Safety of new Biological Therapies for Psoriasis," Arch Dermatol. Res., 298: 7-15 (2006); and *Mease*, et al., at ii78, ii81. It is also known to one skilled in the art that TNF-α plays a pivotal role in psoriasis and that p38 is activated in lesional psoriatic skin. C. Johansen, et al., "Protein Expression of TNF-α in Psoriatic Skin is Regulated at a posttranscriptional Level by MAPK-Activated Protein Kinase 2," The Journal of Immunology, 176, 1431-1438, 1431 (2006); and C. Johansen, et al., "The Mitogen-Activated Protein Kinase p38 and ERK ½ are Increased in Lesional Skin," Brit. Journal of Dermatology, 152, 37-42 (2005).

P38-α signaling and TNF-α regulation has been shown to be involved in the pathogenesis of inflammatory bowel disease-- i.e., Crohn's disease and ulcerative colitis. G.H. Waetzig, et. al., "p38 Mitogen-Activated Protein Kinase is Activagted and Linked to TNF-α Signaling in Inflammatory Bowel Disease," The Journal of Immunology, 168, 5342-5351 (2006).

Lastly, studies have identified p38 MAPK as a novel therapeutic target to overcome drug resistance and patient outcome in multiple myeloma. T. Hideshima, et al., "Targeting p38 MAPK Inhibits Multiple Myeloma Cell Growth in Bone Marrow Milieu," Blood, 101, 703-705 (2003); and T.A. Navas, et. al., "Inhibition of p38-α MAPK enhances Proteasome Inhibitor-induced Apoptosis of Myeloma Cells by Modulating Hsp27, Bcl-X_L, Mcl-1 and p53 Levels *in vitro* and Inhibits Tumor Growth *in vivo*," Leukemia, 1-11 (2006).

Consequently, one skilled in the art would recognize that the compounds taught by the present invention would inhibit p38-α and affect TNF-α regulation in a similar manner as described in the above-cited references, such that the instant specification is enabling for treating the indications identified in Claims 20 and 22. As a result, applicants believe that the rejection under the first paragraph of 35 U.S.C. § 112 has been overcome and should be kindly removed.

Fees

If it is determined that a fee is due, please charge same to Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company.

SUMMARY

In view of the foregoing comments and amendments, applicants kindly request reconsideration of the application. Applicants believe the case is now in condition for allowance and respectfully request the Examiner to pass the case to issue at an early date.

Respectfully submitted,

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Date: July 12, 2006